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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,259	10/25/2005	Mitsuo Ochi	T0509 70012US00	3132

23628 7590 05/28/2010

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
BURK, CATHERINE E	
ART UNIT	PAPER NUMBER
3735	
MAIL DATE	DELIVERY MODE
05/28/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,259	OCHI, MITSUO	
	Examiner	Art Unit	
	CATHERINE E. BURK	3735	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *PTO-90C Communication*.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10554259	10/25/2005	OCHI, MITSUO	T0509 70012US00

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
CATHERINE E. BURK	
ART UNIT	**PAPER**
3735	20100518

DATE MAILED:

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Commissioner for Patents

The examiner spoke with applicant's representative, Michael Siekman, in a telephone call placed on May 19th, 2010 concerning the notice of non-compliance which was mailed on January 6th, 2010. This notice was mailed in response to applicant's reply, which was received on September 15th, 2009, to the non-final office action mailed on April 15th, 2009. It was determined that the notice of non-compliance was in error. Accordingly, the notice of non-compliance is hereby vacated. As a result, claims 15-65 were compliant and should have been examined on the merits. In the response to the notice of non-compliance, applicant withdrew claims 15-65 and added new claims 66-117. However, upon vacation of the notice of non-compliance, the examiner recommended applicant submit a supplemental response cancelling claims 66-117 and resubmitting claims 15-65 for consideration by the examiner. Applicant's representative agreed to submit the supplemental response re-presenting claims 15-65 for examination.

/Charles A. Marmor, II/
Supervisory Patent Examiner, Art Unit 3735

/C. E. B./
Examiner, Art Unit 3735

DETAILED ACTION

This Office action is responsive to the Amendment filed on May 21st, 2010. The examiner acknowledges the cancellation of claims 1-14 and 66-117. Claims 15-65 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 43-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. The term "sufficient" in claims 43 and 62 and the term "effective" in claim 58 are a relative terms which render the claims indefinite. The terms "sufficient" and "effective" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how long the magnetic particles need to be held at the injury site in order to be sufficient to induce tissue repair or to treat dementia or to be effective in treating the tumor. Claims 44-57 depend from claim 43, claims 59-61 depend from claim 58, and claims 63-65 depend from claim 62.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 34, 35, 43, 44, 46, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Ludwig (US 2003/0082148 A1).

6. Claims 34 and 35, 43, 44, 47; Ludwig discloses a method comprising administering a magnetic cell into a subject having an injury or lesion in need of repair. The magnetic cell comprises a cell, a magnetic particle bound to the cell via a linker, which may be a peptide (claims 35 and 44) [0069-70], and a therapeutic substance for controlling the activity of the magnetic cell [0087]. The therapeutic substance constitutes a drug. A magnetic field is applied to attract the magnetic cell toward the injury site in the subject in an amount or duration sufficient to induce tissue repair (claim 43) [0111 and 0145]. This may be accomplished by implanting a magnetic or magnetizable blood contacting surface at the injury site [0061]. Once the cell has been targeted to the injury site, the therapeutic substance is released from the cell (claim 47) [0085]. This therapeutic substance can control the activity of the magnetic cell by causing the cell to have an increased affinity for the blood contacting surface once the magnetic cell has been recruited to the area of injury [0087] (claim 34).

7. Claim 46; the magnetic particles are encapsulated in a polymeric matrix which may comprise RGD peptides; these peptides are used to attach the magnetic particles to surface integrins on the target cells [0069-70]. Therefore it is inherent that the cells express integrin.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludwig.

10. Claims 41 and 42; Ludwig discloses a therapeutic substance may be expressed by the cell once the cell is recruited to the injury site for controlling the activity of the cell [0085 and 87] but fails to explicitly disclose the activity is differentiation of proliferation. However, Ludwig does disclose including therapeutic substances on the blood contacting surface to which the magnetic cells are attracted and expressing these substances to control the differentiation and proliferation of the magnetic cell once the cell is recruited thereto [0097]. It would have been obvious to one of ordinary skill in the art at the time of the invention that the therapeutic substance expressed by the cell once recruited to the injury site in the method disclosed by Ludwig could be a drug that controls the differentiation and/or proliferation of the cell because Ludwig already discloses including such a substance at the injury site on the blood contacting surface. Incorporating the drug into the polymer matrix of the magnetic particle or into the cell itself would be an obvious modification to this method because it would accomplish the same task of localizing such a drug to the injury site.

11. Claims 15, 16, 18, 20-25, 27, 29, 30, 32, 36, 45, 48, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludwig in view of Stickel (The Journal of Cell Biology 107: 1231-1239, September 1988).

12. Claims 15, 16, 20, 21; Ludwig discloses a culture of cells that are magnetically modified so as to enable recruitment of the modified cells by a magnet when they are injected into a patient's bloodstream. The magnetic particles may be attached to the surface of the cell through

a number of different linking mechanisms [0062]. Ludwig discloses modifying the surface of the magnetic particles to have an affinity for the targeted cells for example by encapsulating each magnetic particle within a polymeric matrix. The polymeric matrix may comprise proteins or peptide sequences, such as RGD peptides which provide sites of attachment for target cell surface integrins [0069-70]. Since the magnetic particles are modified to have an affinity for cell surface integrins, it is inherent that the cells to which they are bound are cells which expresses integrin (claims 16 and 21). Ludwig is silent as to the RGD sequence of the encapsulating polymer being an RGDS or GRGDS sequence. However, Stickel discloses a type of RGD sequence, GRGDS, which has a high affinity for cell integrins (p. 1237, left column). It would have been obvious to one of ordinary skill in the art at the time of the invention to use a peptide having a GRGDS sequence as the RGD peptide disclosed by Ludwig, because Stickel discloses that GRGDS mimics the cellular binding domain of many adhesive proteins found in the extracellular matrix (abstract) (claims 15 and 20).

13. Claims 24, 25, 30, 36, and 45; Ludwig discloses a method of localizing a magnetic cell to a site in a subject [0057]. The method comprises administering a magnetic cell into a subject having a disease or lesion [0059 and 0111] and applying a magnetic field at or near the site of the disease or lesion so as to localize the magnetic cells at the site. The magnetic field may be applied outside the body or by embedding a magnet inside the body [0128]. Ludwig further discloses the magnetic cell comprises a cell bound to a magnetic particle that has been coated with a peptide having an RGD amino acid sequence; the RGD sequence has an affinity for cell surface integrins that are expressed by the target cells (claims 25 and 30) [0069-70]. Ludwig is silent as to the RGD sequence of the coating polymer being an RGDS or GRGDS sequence.

However, Stickel discloses a type of RGD sequence, GRGDS, which has a high affinity for cell integrins (p. 1237, left column). It would have been obvious to one of ordinary skill in the art at the time of the invention to use a peptide having a GRGDS sequence as the RGD peptide disclosed by Ludwig, because Stickel discloses that GRGDS mimics the cellular binding domain of many adhesive proteins found in the extracellular matrix (abstract) (claim 24, 36, and 45).

14. Claims 18, 22, 27, 32, and 48; Ludwig in view of Stickel are silent as to the amount of peptide coating the magnetic particle. However, differences in concentration will not generally support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 and In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). Therefore, claiming a ratio of 3ng-6.6μg of peptide for every 1mg of magnetic particle does not distinguish over prior art disclosed by Ludwig in view of Stickel, whom disclose a magnetic particle coated with the claimed peptide and attached to a cell surface, because determining the optimum range of a specific parameter in an otherwise equivalent system involves only routine still in the art.

15. Claim 23 is a product by process claim. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re

Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Ludwig discloses that the magnetic cells may be introduced into a patient's bloodstream after having been harvested from an external source [0014]. It is obvious that these cells are cultured in vitro for some amount of time which may include a time of up to 21 days. Furthermore, since the product disclosed by Ludwig in view of Stickel is a magnetic cell meeting all the structural limitations of claim 22, adding the limitation that the cell is grown in vitro for up to 21 days fails to distinguish over this prior art unless applicant can provide evidence on the record that growth for up to 21 days in vitro would result in a patentably distinct structural difference between the prior art magnetic cell and the claimed magnetic cell.

16. Claim 29; Ludwig discloses the blood-contacting surface may be constructed to degrade over a period of 1 week up to 12 months, during which time the magnetic cell will be retained at the disease site.

17. Claim 49; a therapeutic substance for controlling the activity of the magnetic cell [0087]. The therapeutic substance is considered to be a drug. Once the cell has been targeted to the injury site, the therapeutic substance is released from the cell; this constitutes administering the drug [0085].

18. Claims 17, 19, 26, 28, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludwig in view of Stickel as applied to claim 15 above, and further in view of Chen (US 5921244 A).

19. Claims 17, 19, 26, 28, 31, and 33; Ludwig discloses the magnetic cell may be engineered to express a therapeutic substance, which may be a drug, at the blood contacting surface [0059]

but Ludwig in view of Stickel fail to specifically disclose that the magnetic particle comprises the drug. However, Chen discloses a method of applying therapy to a damaged or diseased tissue region using magnetic particles. These magnetic particles have been coated with a polymeric material that binds to a desired drug so that when the magnetic particles are injected into the body, they can carry the drug to the desired treatment region so that the drug may be concentrated there (col. 2, lines 42-51 and col. 6, lines 17-25). It would have been obvious to one of ordinary skill in the art at the time of the invention to bind a drug to the surface of the magnetic particle disclosed by Ludwig in view of Stickel, similar to the drug binding technique disclosed by Chen, because Chen teaches this is a known method of concentrating a therapeutic substance at a treatment region when magnetic particles are being used.

20. Claims 37-40, 50-57 rejected under 35 U.S.C. 103(a) as being unpatentable over Ludwig in view of Kubo (International Journal of Oncology 17: 309-315, 2000).

21. Claims 37, 38, 50, and 54; Ludwig discloses the magnetic particle may also be in the form of a liposome that encapsulates magnetic material [0064] but fails to disclose the therapeutic agent is also contained in the liposome. However, Kubo discloses that liposomes can be used to localize a therapeutic agent, or drug, to a specific area of tissue by incorporating a drug into a magnetized liposome and using an external or embedded magnet to guide the drug/liposome complex (abstract) (claims 37, 38, 50, and 54). It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the therapeutic agent into the magnetic liposome in the method disclosed by Ludwig, as taught by Kubo, because Kubo teaches is it known in the art to use magnetic liposomes as drug delivery vehicles.

22. Claims 51 and 55; a plurality of magnetic particles can be attached to the surface of the cell because there will be more than one site of integrin expression on the cell membrane, therefore the drug may be contained in a second magnetic particle.

23. Claims 39, 40, 52, 53, 56, and 57; Ludwig discloses that the magnetic particles, which have been modified in view of Kubo to contain a drug, can either be added to the surfaces of the cells in vitro and then injected into the patient [0062] (claims 39, 52, and 56), or injected separately from the cell so that the magnetic particles containing the drug bind to the cells in vivo [0014 and 0164] (claims 40, 53, and 57).

24. Claims 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludwig in view of Stickel as applied to claim 15 above, and further in view of Kubo.

25. Claims 58-61; Ludwig in view of Stickel, as outlined above, disclose administering a magnetic cell to a subject and directing the magnetic cell to an injury region using an applied magnetic field. The magnetic field may be applied by an external magnet or an embedded magnet [0128] (claims 59 and 60). The magnetic cell comprises a cell bound to a magnetic particle which may comprise a liposome that encapsulates magnetic material. The magnetic particle may be bound to the cell via a peptide linker having a GRGDS amino acid sequence incorporated on the surface thereof. The GRGDS sequence has an adhesive affinity for integrins on the surface of the cell. Ludwig also discloses the magnetic cell may comprise a therapeutic agent. Ludwig in view of Stickel fail to disclose using the method to treat a tumor and therefore fail to disclose the magnetic particle comprises an anti-cancer drug and that the magnetic cell is localized near the site of a tumor.

However, Kubo discloses liposomes can be used to localize a therapeutic agent, such as the anti-cancer drug Adriamycin (which is the trade name for Doxorubicin) (claim 61) to a tumor by incorporating the drug into a magnetic liposome and using an external or embedded magnet to guide the drug/liposome complex (abstract). It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method disclosed by Ludwig in view of Stickel to treat a tumor because Kubo teaches it is known to use magnetically tagged liposomes to deliver drugs to tumor sites (claim 58). Furthermore, when using the method disclosed by Ludwig in view of Stickel to treat a tumor, it would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate a drug such as doxorubicin into the magnetic liposome because it is a well-know anti-cancer drug that is known to be deliverable to tumors via liposomes, as taught by Kubo.

26. Claims 62, 63, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ludwig in view of Handy (US 2003/0032995 A1).

27. Claims 62 and 65; Ludwig discloses a method comprising administering a magnetic cell into a subject and applying a magnetic field to attract the magnetic cell toward a desired tissue region in the subject for a desired amount of time [0111 and 0145] wherein the magnetic cell comprises a cell and a magnetic particle bound to the cell via a linker [0069-70]. Ludwig fails to disclose using the method to treat dementia. However, Handy discloses a method of treating a patient comprising administering a composition of magnetic particles into a patient and using a ligand -640- bound to the magnetic particles to bind to specific proteins in the body. When a magnetic field is applied to the magnetic particles bound to these proteins, the proteins can be

denatured or otherwise deactivated. It is known that amyloid protein buildup in the brain is part of the pathology of Alzheimer's disease, therefore configuring the magnetic particles to bind amyloid proteins will lead to their deactivation upon application of a magnetic field [0182-0185]. In this method, the ligand which binds amyloid protein can be considered to be a dementia therapeutic agent (claim 65). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method disclosed by Ludwig to include the step of causing the magnetic particles to bind to amyloid proteins in the brand in order to treat dementia, as taught by Handy, because Handy teaches that treating dementia is a known application of targeted magnetic particles (claim 62).

28. Claim 63; the magnetic particles are encapsulated in a polymeric matrix which may comprise RGD peptides; these peptides are use to attach the magnetic particles to surface integrins on the target cells [0069-70]. Therefore it is inherent that the cells express integrin.

29. Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ludwig in view of Handy as applied to claim 63 above, and further in view of Stickel.

30. The linker between the magnetic particle and the cell disclosed by Ludwig may comprise proteins or peptide sequences, such as RGD peptides on the surface of the magnetic particle which provide sites of attachment for target cell surface integrins [0069-70] but Ludwig is silent as to the RGD sequence being an RGDS or GRGDS sequence. However, Stickel discloses a type of RGD sequence, GRGDS, which has a high affinity for cell integrins (p. 1237, left column). It would have been obvious to one of ordinary skill in the art at the time of the invention to use a peptide having a GRGDS sequence as the RGD peptide disclosed by Ludwig,

because Stickel discloses that GRGDS mimics the cellular binding domain of many adhesive proteins found in the extracellular matrix (abstract).

Response to Arguments

31. Applicant's arguments with respect to claims 15-65 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE E. BURK whose telephone number is (571) 270-7130. The examiner can normally be reached on Monday-Thursday 8:30 am - 7:00 pm EDT.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Charles Marmor II can be reached on (571) 272-4730. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Charles A. Marmor, II/
Supervisory Patent Examiner
Art Unit 3735

/C. E. B./
Examiner, Art Unit 3735